Ketamine for Treatment-Resistant Depression

Background

Ketamine hydrochloride, originally a veterinary anesthetic, was called a "dissociative anesthesia" in a 1966 study report on its use in human anesthesia, (Li & Vlisides, 2016) and granted Federal Drug Administration (FDA) approval in 1970. (*Ketalar Label*, n.d.) Ketamine is a relatively safe drug in the anesthesia setting, with the ability to produce profound analgesia, dissociation from sensory input, and sedation, while airway reflexes and respiratory drive remain intact.(Li & Vlisides, 2016)

Due to its dissociative and psychotomimetic effects, ketamine emerged as a popular party drug in the 1990s. Coincidentally, there was also growing public and clinician demand for alternative treatments for both chronic pain and depression. Ketamine was found to produce strong analgesia during infusion, with several studies showing long-term analgesic effects 3-months after a prolonged infusion. (Niesters et al., 2014) In 2000, an intriguing study (Berman et al., 2000) showed that subanesthetic doses of ketamine produced a profound and rapid antidepressant response. This led to additional studies confirming this rapid effect. Specifically, IV ketamine, delivered at a dose of 0.5 mg/kg over 30-40 minutes, induced rapid reduction in depressive symptoms in about 60-75% of patients. (Henderson, 2016) These positive findings fed public and clinician demand for alternative treatments for depression, but the potential for abuse and addiction presents barriers to its widespread use in the psychiatric setting.

The Need for Alternative Treatments for Treatment-Resistant Depression

Major depression (MDD) disorder has a lifetime prevalence of 11% to 7.5%, with higher prevalence in women (2:1) and if untreated, increases risk for disability, decreased quality of life, and suicide (Carboni et al., 2021). The United States spends 200 billion USD annually, more than for diabetes or cancer (Ionescu et al., 2015) For the past 50 years, pharmaceutical options have been dominated by monoaminergic agents (affecting serotonin, norepinephrine, and/ or dopamine) which require weeks to months to work, and provide relief for only about two-thirds of those treated. (Carboni et al., 2021). Alternatives are needed for patients with treatment-resistant depression (TRD), defined as requiring "a minimum of two prior treatment failures and confirmation of prior adequate dose and duration." (Gaynes et al., 2020)

IV Ketamine and Intranasal Esketamine

Responding to demand for alternative treatments, IV ketamine clinics started to appear around 2014, and there are now dozens of such clinics in the US. (Goldhill, n.d.) Based on its approved use as an anesthetic, clinicians provide ketamine infusions "off-label" for indications such as pain and depression. While ketamine is a racemic mixture of two enantiomers (S-enantiomer and R-enantiomer), an S-enantiomer formulation, called esketamine, was packaged in an intranasal device and patented, then approved by the FDA in 2019 for use in conjunction with an oral antidepressant, in adults with TRD. In 2020, approval was extended to include its use in adults with major depressive disorder (MDD) experiencing acute suicidal ideation or behavior; again, in conjunction with an oral antidepressant. The drug remains a Drug Enforcement Administration Schedule III medication, and must be administered following unique stipulations. (Commissioner, 2020)

Ensuring Safety and Quality

The American Psychiatric Association (APA), in 2017, published a consensus statement on the use of IV ketamine in mood disorders, acknowledging the potential benefits and risks associated with ketamine and the limitations of the research. The statement discusses patient selection and components of pretreatment evaluation, clinician experience and training, treatment setting considerations, drug dosing and delivery, efficacy, safety, and patient education and follow-up. (Sanacora et al., 2017) Then, in 2019, the American Association of Nurse Anesthesiology (AANA), along with the American Psychiatric Nurses Association (APNA), in a joint position statement, supported a "patient-centered, interdisciplinary approach to managing patients who suffer from psychiatric disorders and may benefit from ketamine infusion therapy," and recognized "the professional scope of practice and expertise of certified registered nurse anesthetists (CRNAs), psychiatric mental health registered nurses (PMH RNs), and psychiatric mental health advanced practice registered nurses (PMH APRNs)." The statement links to a *Ketamine Treatment Considerations Checklist*, (*Ketamine Checklist*, n.d.) to assist clinicians in complying with professional scope and standards of practice, applicable federal and state laws, facility policies, and current clinical best practices when delivering off-label ketamine to psychiatric patients. It must be emphasized that laws and scopes of practice vary between states, but in every case, each professional brings expertise, enhanced by collaboration, to safely deliver off-label ketamine for depression. (*Ketamine-Infusion-Therapy-for-Psychiatric-Disorders-and-Chronic-Pain-Management.Pdf*, n.d.) (*Apna-Aana-Joint-Statement-on-Ketamine.Pdf*, n.d.)

Mechanisms of Action

Ketamine has effects on several neurotransmitter and neuromodulatory systems but most of its known effects appear to be related to its function as an *N*-methyl-D-aspartate receptor (NMDAR) antagonist. NMDAR mediates glutamate, an excitatory neurotransmitter. While ketamine blocks NMDA, it produces a surge of glutamate in the brain. The paradoxical increase of glutamate appears to be due to ketamine's selectivity for binding to NMDAR on gamma-aminobutyric acid (GABA) inhibitory neurons. Blocking NMDAR on GABA neurons means that glutamate is not stimulating these inhibitory neurons, resulting in a glutamate surge. This transient glutamate burst corresponds to the drugs dissociative and psychotomimetic effects that occur when ketamine is at peak concentration in the brain. Glutamate also stimulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which is associated with increased synaptic connections on excitatory neurons, and is believed to contribute to long-term memory formation. AMPA stimulation also appears to produce a downstream effect, causing an increase in neurotrophic factor (BDNF), and in mammalian target of rapamycin complex 1 (mTORC1) signaling. BDNF and mTORC1 are involved in regulating the growth of neurons in the brain, and prolonged stress is associated with reduced BDNF and inhibited mTORC1 signaling in the prefrontal cortex (PFC). Depressive-like symptoms can be induced in animals by reducing BDNF or inhibiting mTORC1 (Abdallah et al., 2016). While acute stress promotes synaptic survival and strength, resulting in behavioral learning and adaptation ("The Dazzling Promise of Ketamine," n.d.), prolonged stress causes reduced dendritic spine density, retraction of spines, overall reduced dendritic branching, and synaptic depression, in the PFC

and hippocampus. Brain imaging studies of depressed patients show decreased volume in PFC and hippocampus ("The Dazzling Promise of Ketamine," n.d.). It is hypothesized that ketamine-induced synaptogenesis allows the brain to continue to heal from depression even after the drug has cleared.

Pharmacokinetics and Pharmacodynamics

Bioavailability of ketamine is up to 100% with intravenous delivery and as low as 20% with oral administration. Intranasal delivery, at an appropriate dose, has been shown to be comparable to the common dosing formula for IV ketamine, at 0.5 mg/kg. Ketamine is eliminated via the kidneys and has an elimination half-life of 2.5 hours. Ketamine's antidepressant effects emerge about 4 hours after intravenous administration, well after the drug has been cleared from the bloodstream. Depressive symptoms usually return to baseline levels within 1 to 2 weeks. However, growing evidence suggests that repeated administration can extend ketamine's antidepressant effects. Current data suggests that up to six 0.5 mg/kg intravenous infusions, administered three times per week for 2 weeks, are safely tolerated and can prolong the antidepressant effects. However, there is still uncertainty on ketamine's optimal dosing, and the safety of long-term treatment. Recent open-label studies have shown that smaller doses (e.g., 0.2 mg/kg) yield antidepressant effects that are comparable to the typical 0.5mg/kg intravenous dose (Abdallah et al., 2016). Ketamine is associated with few drug interactions, and there are no known contraindications when combined with antidepressants, benzodiazepines, or other psychotropic medications. (*Ketamine-Infusion-Therapy-for-Psychiatric-Disorders-and-Chronic-Pain-Management.Pdf*, n.d.)

Adverse Events

Ketamine has minimal effect on respiratory drive even at anesthetic doses. Short-term administration appears to be relatively safe, and adverse effects tend to resolve spontaneously after the drug is administered. The literature does report several instances of transient apnea when IV ketamine was administered through rapid IV push (Rosenbaum et al., 2021). A review of 60 studies found that dissociation and psychotomimetic effects were reported in 70% of these studies, with IV ketamine twice as likely as non-IV ketamine to cause these effects (Short et al., 2018). The dissociative effects occur 40 to 60 minutes after starting the infusion, resolve within 4 hours, appear to be dose-related, and tend to diminish with repeat infusions (Rosenbaum et al., 2021). There is a mild cardiovascular effect with an average systolic pressure blood pressure increase of 20 mmHg and a diastolic increase of 8-13 mmHg. Pulse rate has also been shown to increase transiently, and cardiovascular effects tend to normalize within 2 hours. Patients have also experienced palpitations, and chest pain and pressure, which usually resolved within 90 minutes. Other transient effects include sedation, anxiety, blurred vision, dizziness, headache, nausea, and vomiting (Rosenbaum et al., 2021).

There are few studies looking at the long-term adverse effects of ketamine. Abuse and addiction are potential hazards, and most studies exclude patients with substance abuse disorders. Animal studies and studies of ketamine abusers have found adverse effects on cognitive function. Ketamine abuse is associated with bladder toxicity, which can lead to scarring and the need for surgery. Ketamine abuse is also associated with hepatotoxicity, and

patients with moderate to severe hepatic dysfunction or high-risk coronary artery disease are at increased risk for adverse events following ketamine infusion. (Short et al., 2018)

Contraindications

The prescribing information for IV ketamine states that ketamine is contraindicated for "those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug." It warns against using IV ketamine in chronic alcoholic and/or alcohol-intoxicated patients, and because of the possibility of inducing psychosis, it is not recommended in patients with schizophrenia. It should be used with extreme caution in patients with elevated cerebrospinal pressure, as there have been reports of elevated cerebrospinal fluid pressure following anesthetic doses of IV ketamine. Safe use in pregnancy and in breastfeeding patients has not been established and is therefore not recommended (*Ketalar Label*, n.d.).

Patient Education and Informed Consent

The APA, AANA, and APNA, all emphasize the importance of patient education and informed consent, which should include a discussion on the benefits of treatment, the lack of extensive high-quality evidence supporting efficacy and safety, especially in long-term treatment, the drug's "off-label" status, and alternative treatments. The effects of treatment should also be discussed, as well as the risks and potential adverse effects. The information should be augmented with written material and the informed consent should be documented (Sanacora et al., 2017).

Administering IV Ketamine

Dosing

The APA makes no definitive recommendations on dosing but recognizes the commonly used dose of 0.5mg/kg over 40 minutes as "standard" and suggests that deviations from this dosing should be pointed out to the patient as part of the informed consent process. They do acknowledge that variations to the standard dosing may be appropriate. They acknowledge that greater hemodynamic changes were seen in patients with body mass index of 30 or more receiving the standard dose, and therefore suggest that dosing in these patients be based on calculated ideal vs. actual body weight (Sanacora et al., 2017).

Monitoring IV Ketamine

The APA, AANA, and APNA, recommend that all treatment centers contain the ability to monitor cardiovascular and respiratory function. Clinics should be equipped to monitor electrocardiogram, blood pressure, oxygen saturation, and end-tidal CO2. Mental status should be assessed during and post-infusion using a standardized assessment tool (i.e., Modified Observer's Assessment of Alertness/Sedation Scale) to determine level of consciousness. Clear hemodynamic and behavioral parameters for stopping the infusion should be defined, and protocols in place to manage hemodynamic emergencies. Treatment settings should have advanced cardiac life support (ACLS) capabilities, including an appropriately stocked crash cart,

and ACLS-certified personnel on site during the infusion and post-infusion monitoring period. There should be at least one person skilled in advanced airway management, with airway management supplies and supplemental oxygen, available. Because the dissociative effects may cause some patients to act out, there should be restraints available and a restraint protocol in place (Sanacora et al., 2017).

Monitoring should continue post-infusion until the patient returns to baseline physiological and mental status. The patient should be advised not to drive or use heavy machinery and to avoid drugs and alcohol for 24 hours after the infusion, and there should be a responsible adult available to transport the patient home after the infusion. Follow-up procedures should be reviewed prior to discharge and the patient should be given the means to rapidly contact a clinician after discharge, in case of emergency. In patients receiving multiple infusions, follow-up visits should include questions about urinary discomfort, cognitive function, and substance use, given the known and suspected risks for cognitive impairment, cystitis, and abuse, associated with long-term use of ketamine (Sanacora et al., 2017).

Intranasal Esketamine

Intranasal esketamine has been approved by the FDA, in conjunction with an oral antidepressant, for treatment of TRD, and MDD with suicidal ideation or behavior. The medication is available only through a restricted distribution system, required by the FDA, called the Risk Evaluation and Mitigation Strategy (REMS), because of the risks for both "serious adverse outcomes resulting from sedation and dissociation," and "use and abuse" of esketamine. The medication can only be delivered in a certified treatment setting under the direct supervision of certified providers. The prescribing information suggests recommended dosage regimens, which can be tailored to the individual. Patients self-administer intranasal doses under supervision at the clinic, remain there for at least 2 hours for monitoring, and are discharged with a responsible adult, who can drive them home after treatment. All inpatient and outpatient facilities, pharmacies, and providers delivering esketamine, must be certified by REMS. Patients treated outpatient must be enrolled in the REMS program and patient monitoring forms submitted after each treatment. (*SPRAVATO® REMS (Risk Evaluation and Mitigation Strategy)*, n.d.) The prescribing information describes appropriate monitoring before, during, and after treatment, and the risks are similar to those with IV ketamine. Patients should be advised to avoid food and drinks prior to treatment due to potential nausea and vomiting. They should be instructed to use any prescribed nasal steroids or decongestants at least 1 hour before esketamine treatment. Instructions for medication delivery are clearly described in the prescription insert (*SPRAVATO-Pi.Pdf*, n.d.)

Key Considerations

- IV and intranasal ketamine may provide relatively safe and rapid relief of TRD and MDD with suicidal ideation and behavior, and repeated treatments may prolong the beneficial effect, but the safety profile of prolonged ketamine use has not been established.

- While ketamine is relatively safe, potential serious short-term adverse effects include dissociation, sedation, psychotomimetic effects, and elevated blood pressure, while long-term treatment imposes risk for bladder and liver toxicity, cognitive impairment, and abuse.

- Patients should be treated in facilities with appropriate monitoring and rescuing capabilities, by providers who are well-trained and qualified to administer and monitor the treatments, according to local, state, and federal laws, and professional scope of practice.

- Prior to treatment, patients should be informed of the benefits of treatment, the lack of extensive high-quality evidence supporting efficacy and safety, especially in long-term treatment, the drug's "off-label" status, and alternative treatments. The effects of treatment should also be discussed, as well as the risks and potential adverse effects.

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